REMARKS

Claims 20, 49-51, 56, 57, 59 and 65-67 were pending in the subject application. Applicants have herein canceled claim 50, and amended claims 20, 49, 51, 56, 57, 59, and 65-67. The claims have been amended to specify that the mesenchymal stem cells incorporated with a nucleic acid which encodes a HCN2 channel are "capable of forming a gap junction with a cell of a mammalian heart" and that the cells are introduced "directly" into the mammalian heart. The amendments are fully supported in the specification as follows: claim 20: page 2, line 30 to page 3, line 6; page 17, lines 5-6; page 20, lines 29-31; Figs. 3, 4 and 10; claim 49: page 14, lines 11-12; page 15, lines 1-9; page 26, lines 11-14; Figs. 3, 4 and 10; claim 51: page 14, lines 11-26; page 15, lines 1-9; page 26, lines 11-14; claim 56: page 15, lines 1-9; claims 57 and 66: page 15, lines 1-9; page 26, lines 11-14; Figs. 3, 4 and 10; claims 59 and 67: page 15, line 28 to page 16, line 2; Fig. 3; and claim 65: page 9, lines 4-9; page 15, lines 1-9; page 17, lines 5-6; page 26, lines 11-14; Figs. 3, 4 and 10. Thus, Applicants maintain that these amendments do not present new matter. Accordingly, Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 20, 49, 51, 56, 57, 59 and 65-67, as amended, will be pending and under examination.

Applicants again thank the Examiner and his supervisor for the courtesy extended during the interview held on January 19, 2007, a Summary of which was prepared by the Examiner and attached to the February 13, 2007 Office Action. The remarks which follow reflect, in part, the discussions held during the January 19, 2007 interview.

Rejection of claims 49-51, 56-57, 59 and 65-67 under 35 U.S.C. §112, First Paragraph (Enablement)

The Examiner rejected claims 49-51, 56-57, 59 and 65-67 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner stated that, as a first issue, the breadth of the claims encompass expressing a functional ion channel in any syncytial structure whereas the specification provides guidance for using hMSCs as a delivery vehicle only in heart for the expression of HCN2, wherein the HCN2-expressing hMSC is engrafted with recipient cardiomyocytes via formation of gap junctions. Citing Popp et al. (2006) *Stem Cells Express*, pp. 1-25 [published online November 16, 2006], which teaches that MSCs injected directly

into the portal vein of a recipient rat resulted in no engraftment of MSCs in a liver injury model, the Examiner asserted that a general method of site-specific administration of MSCs as a delivery vehicle in any syncytial structure would not result in engraftment or formation of gap junction as contemplated by the breadth of the claims.

Applicants respectfully traverse this rejection but maintain that the cancellation of claim 50 and the amendments to the other rejected claims render this ground of rejection moot.[1] Specifically, Applicants note that claims 49, 51, 57, 65 and 66, as amended herein, recite the site-specific introduction of a HCN2-expressing MSC directly into a mammalian heart and that the introduced MSC are capable of forming gap junctions with the cells of the heart. The introduction of the MSC directly into the heart obviates the purported problem described by Popp et al. (2006) regarding the failure of stem cells injected into a blood vessel to engraft in the targeted organ and form gap junctions. It also precludes any requirement for homing of the transplanted MSCs to the any targeted syncytial structure prior to engraftment or formation of gap junctions.

The Examiner stated that, as a second issue, the scope of invention encompasses a method for inducing pacemaker current and treating a cardiac rhythm disorder in a subject by administering the disclosed genetically modified MSC composition. The Examiner further stated that the breadth of claims 51 requires expression of HCN2 at a therapeutically effective level sufficient to create ion channels for a sustained period in order to treat any cardiac rhythm disorder, but does not provide any specific guidance as to how expression of HCN2 would be achieved at a therapeutically effective level for a sustained period of time using any construct. The Examiner also raised questions regarding whether the differentiation state of MSCs is altered *in situ*, whether such differentiation would affect HCN2 expression or biophysical properties, the host immune response to implanted cells, and the homing mechanism that guides delivered cells to the target site.

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1 Applicants assert that they reserve their right to pursue the canceled subject matter in a continuation application.

In response, Applicants again note that the claims have been amended to recite the site-specific introduction of a HCN2-expressing MSC directly into a mammalian heart and that the introduced MSC are capable of forming gap junctions with the cells of the heart.[2] Applicants contend that the claim amendments now render moot the Examiner's rejection on this second ground. Applicants maintain that at the time the subject application was filed the HCN2 channel was well known and the specification teaches, by incorporation of relevant cited references, the sequences of HCN2 (see paragraphs [0037]-[0048] of the specification). Further, the specification teaches a person skilled in the art methods for isolation of homogeneous populations of MSCs, nucleic acids encoding the HCN2 channel that may be expressed in MSCs to induce or regulate a pacemaker current therein, and the use MSCs expressing a pacemaker ion channel to induce a pacemaker current in a heart.

Moreover, the specification provides a working example of the delivery into a canine heart of hMSCs transfected with a nucleic acid encoding a HCN2 polypeptide, resulting in the expression of functional HCN2 channels and the generation of a stable, idioventricular pacemaker rhythm in the canine heart. (*See* para. 0029 and Fig. 10). The use of a canine model is based on its cardiac size, tractability as a chronic model and similar electrophysiologic properties to those of human. Those skilled in the art would consider Applicants'canine model and working example to provide a reasonable correlation to Applicants'claimed invention (see MPEP 2164.02)

Further, Applicants direct the Examiner's attention to the publication of Plotnikov et al. (2005) *Circulation* 112: II-126 (henceforth "Plotnikov;" submitted as Exhibit A in the March 7, 2006 Amendment), which describes the injection of mHCN2-transfected hMSCs directly into left ventricular (LV) subepicardium of non-immunosuppressed adult dogs. Plotnikov reports that nests of hMSCs were found adjacent to the injection site but not at a distance. As noted by Applicants in their September 25, 2006 Amendment, Plotnikov is a post-filing date reference that describes the results of experiments conducted in accordance with methods disclosed in the specification.

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2 Applicants further note that claim 51 was previously amended to specify that the cardiac disorder to be

To the extent that Plotnikov includes experimental details not described in the specification, Applicants maintain that these details could be determined by a person of ordinary skill in the art without undue experimentation. Applicants maintain that one of skill in the art could readily determine the appropriate concentration of MSC cells which would be effective in the treatment of a particular cardiac disorder or condition. Such concentrations will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. The precise dose of MSCs to be employed in the method of treatment will also depend on the route of administration, and the seriousness of the disease or disorder, and can be decided according to the judgment of the practitioner and each patient's circumstances. Thus, Plotnikov may be properly cited to demonstrate that the disclosures in the specification as filed are sufficient to enable a person skilled in the art to practice the invention being claimed without undue experimentation, *i.e.*, to demonstrate that the disclosure was enabling as of the filing date.

Regarding the Examiner's concern about the sustainability of a therapeutically effective level of HCN2 expression, Plotnikov teaches that physiological function of hMSC-based biological pacemakers occurred in 3-10 days and persisted throughout the 42 days during which the transplanted cells were monitored. In addition, no differentiation of hMSCs was observed in Plotnikov over the 42-day period[3], and there was no humoral or cellular rejection of hMSCs. The latter result is consistent with evidence that hMSCs are immunoprivileged (see Liechty et al. (2000) *Nat Med* 6: 1282-1286, attached as Exhibit 2 in the September 25, 2006 Amendment, at page 1283) and may actually suppress an immune response (see Javazon et al. (2004) *Exp Hematol* 32: 414-425, cited by the Examiner on a PTO-82 form, at page 417, right col.). Accordingly, Applicants maintain that the concerns raised by the Examiner do not undermine the enablement of the claimed invention.

Moreover, Applicants assert that questions regarding the risk of side effects are safety issues to be addressed and resolved in clinical trials. Regarding the degree of safety required

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treated is at least one of conduction block, complete atrioventricular block, incomplete atrioventricular block or sinus node dysfunction.

3 Myogenic MSCs may have the potential to differentiate into cardiomyocytes under certain conditions following transplantation into the heart. See, e.g., U.S. Patent Publication No. 20040087528 ("Levy") and Wang et al. (2000) *J Thorac Cardiovasc Surg* 120: 999-1005 ("Wang"). However, even if, *arguendo*, the transplanted MSCs were to differentiate into cardiomyocytes over a longer period, this would not be deleterious to the presently claimed

under the patent laws, the MPEP states, with respect to satisfying the "how to use" element of the enablement requirement, that "[t]he Applicant need not demonstrate that the invention is completely safe." MPEP § 2164.01(c). This passage also refers the reader to MPEP § 2107.03 (§ 2107 deals with the utility requirement), which states at part V.: "The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs." The MPEP continues: "Thus, while an Applicant may on occasion need to provide evidence to show that an invention will work as claimed, it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness." MPEP § 2107.03 V. (emphasis added) (citing, among others, *In re Hartop*, 311 F.2d 249 (C.C.P.A. 1962), *In re Anthony*, 414 F.2d 1383 (C.C.P.A. 1969), and *In re Watson*, 517 F.2d 465 (C.C.P.A. 1975)).

Thus, Applicants maintain that such safety concerns fall within the ambit of the Food and Drug Administration (FDA) rather than the Patent Office. Certainly, safety data obtainable from clinical trials are not required to satisfy the enablement requirement of a claimed invention. Thus, Applicants maintain that the Examiner's rejections of the claims as lacking enablement based, in part, on perceived safety risks issues is misplaced.

The Examiner stated that, as a final issue, the claimed invention encompasses a method wherein contacting a MSC is effected by injection and microinjection or catheterization. However, the Examiner contended that there were questions concerning the optimal way to introduce cells (local or systemic) for therapeutic purposes, and to ensure their survival following transplantation, the homing of the cells to, appropriate integration of the cells with, host tissues following transplantation, and the potential of transplanted MSCs to differentiate into undesired cell lineages. The Examiner further stated that Potapova et al. (2004) *Circulation Research* 94: 952-959 ("Potopova") at 958 also emphasize the importance of modifying catheters to optimize injection of MSCs without cell injury and destruction.

Applicants respectfully disagree. Again, as noted above, Applicants have amended the

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methods.

claims to recite the site-specific introduction of a HCN2-expressing MSC directly into a mammalian heart and that the introduced MSC are capable of forming gap junctions with the cells of the heart. The introduction of the MSC directly into the heart obviates the purported problem described by Popp et al. (2006) regarding the failure of stem cells injected into a blood vessel to engraft in the targeted organ and form gap junctions. It also precludes any requirement for homing of the transplanted MSCs to the any targeted syncytial structure prior to engraftment or formation of gap junctions.

Regarding the importance of modifying catheters to optimize injection of MSCs without cell injury and destruction allegedly emphasized by Potopova, Applicants note that Potopova merely makes a suggestion that such modification may be necessary: "Before this [catheter] approach is used for hMSCs, catheter modification may need to occur to optimize injection of cells of the size of an hMSC without cell injury or destruction." *See* page 958, right col. (emphasis added). Applicants provided abundant evidence in their September 25, 2006 response to the May 24, 2006 Final Office Action that delivery of hMSCs into the heart by catheterization is viable and is enabled by the specification. *See* pages 14-16 of September 25, 2006 Amendment and Exhibits 5-9 submitted therewith. Applicants maintain that to the extent any modification of catheterization is conducted to optimize delivery of hMSCs into the heart, this modification does not require undue experimentation. Indeed, Applicants note that the Examiner appears to have acknowledged that the specification enables delivery of MSCs into the heart by catheterization when he stated:

> In addition, Applicants['] argument with respect to homogenous population of MSC (page 6, Exhibit 1)[,] SA node cell and delivery of MSC via catheterization is found persuasive and therefore rejection[s] pertaining to these issues are withdrawn.

See page 10, first paragraph, of the Office Action (emphasis added).

Based on the above remarks, Applicants maintain that the specification as filed enables one skilled in the art to practice the now claimed invention employing only routine experimentation. Accordingly, Applicants respectfully request that the present ground of rejection be withdrawn.

Rejection of claims 20, 49-50, 57 and 65-67 under 35 U.S.C. §103(a) (Obviousness)

The Examiner rejected claims 20, 49-50, 57-584 and 65-67 under 35 U.S.C. §103(a) as allegedly unpatentable over Levy, Marban et al. (U.S. Patent Application Publication No. US2004/0254134, published February 16, 2004; effective filing date February 29, 2002; henceforth "Marban"), Jansen et al. (U.S. Patent No. 6,979,532, issued December 27, 2005, effective filing date February 12, 2000; henceforth "Jansen"), and Wang.

The Examiner acknowledged that Levy does not teach administering a composition of MSCs comprising HCN2. However, the Examiner stated that Levy generally embraces the idea of delivering genetically modified MSC comprising a therapeutic (*e.g.*, a mutated ion channel) for the treatment of cardiac disorders. The Examiner also stated that Marban discloses that a composition of modified cells comprising cardiac myocardial cells generated from differentiated stem cells, such as embryonic bone marrow cells, could be implanted in cardiac tissue to induce or modulate pacemaker activity in a subject. The Examiner conceded, however, that Marban does not teach the use of a composition of MSCs comprising HCN2. The Examiner further stated that Jansen teaches a process comprising determining the membrane potential of mammalian cells that express HCN2 but does not explicitly teach a composition of MSCs comprising HCN2. In addition, the Examiner stated that Wang teaches that MSCs administered to the heart show growth potential in a myocardial environment, and also teaches the formation of gap junctions, suggesting that cells derived from marrow stromal cells, as well as native cardiomyocytes, are connected by intercalated disks. Again the Examiner conceded that Wang does not teach a composition of MSCs compromising HCN2.

The Examiner asserted that it would have been obvious for one of ordinary skill in the art at the time of invention to modify the MSCs taught by Levy to include other ion channels such as HCN2 taught by Marban, for using MSCs as delivery vehicles to express HCN2 in mammalian heart for pacemaker activity. The Examiner contended that one of ordinary skill in the art would have been motivated to combine the teachings of Levy, Marban, Jansen and Wang, and would have a reasonable expectation of successfully practicing the method and

4 Claim 58 was previously cancelled.

composition comprising MSCs incorporated with HCN2 or other ion channel gene. The Examiner therefore concluded that the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Applicants respectfully disagree. Applicant notes that in accordance with M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness. Applicant maintains that the Examiner has failed to establish a *prima facie* case of obviousness for the reasons set forth below.

Applicants have amended the claims to recite the site-specific introduction of a HCN2-expressing MSC directly into a mammalian heart and that the introduced MSC are capable of forming gap junctions with the cells of the heart. Applicants maintain that the cited references do not, alone or in combination, disclose or suggest the subject matter encompassed by the claims as amended.

First, it should be noted that Levy discloses a general method of "reverse gene therapy" wherein a dominant negative form of a protein is expressed to alleviate a disease or disorder. Gene therapy methods have typically involved the delivery of a nucleic acid which encodes a normal, i.e., wild type, protein. In contrast, "reverse gene therapy" involves the delivery of a nucleic acid which encodes a pathogenic mutant protein normally expressed only in abnormal tissue. The word "reverse" in reverse gene therapy emphasizes a nucleic acid construct which would normally be harmful if expressed in one physiological setting but when delivered to a different diseased physiological site acts to achieve a beneficial (reverse) effect in that different setting. Specifically, in ¶ [0053] of Levy, the is stated that " the nucleic acid encodes a therapeutic gene product which is usually only expressed in cells of an abnormal tissue which is not afflicted with the same disease or disorder. Such abnormal tissues include, for example, tissues afflicted with a different disease or disorder than the one being alleviated by reverse gene therapy."

With regard to the treatment of cardiac disorders, Levy specifically teaches the expression of a mutant HERG protein or a mutated subunit of HERG, Q9E-hMirp1. For example, Levy teaches that the HERG (A561V) mutation is responsible for one of the forms of the Long QT

Syndrome, a hereditary disorder associated with episodes of ventricular arrythmias and a risk of sudden death (see, [0079] of Levy). Nevertheless, Levy teaches that the expression of such a mutant HERG protein can be used to treat patients afflicted with re-entrant atrial flutter (see, [0081] of Levy). Levy fails to teach the expression of any HCN channel, mutant, much less wild type.

Second, a review of Marban indicates that this reference, like the Levy reference, also focuses on the recombinant expression of dominant negative forms of proteins for treatment of cardiac disorders. Specifically, Marban teaches the expression of dominant-negative Kir2 constructs (see [0052] of Marban), as well as dominant negative HCN channels (see [0061] of Marban). Marban teaches that preferred methods of the invention include dominant negative suppression of Kir-2 encoded potassium channels in the ventricle to produce spontaneous, rhythmic electrical activity (see, [0016] of Marban). Another example of a dominant-negative construct for use in accordance with the invention, as taught by Marban, is a mutant HCN channel that is capable of suppressing the normal HCN-encoded pacemaker current (see, [0061] of Marban).

Applicants maintain that, given that both Levy and Marban teach the expression of non-functional, or dominant negative forms of proteins, these references in fact teach away from the present invention which is directed to the expression of functional HCN channels for treatment of cardiac disorders.

Although, Jansen teaches the expression of functional HCN channels in CHO and HEK cells this is contrary to the teachings of Levy and Marban. Furthermore, it is noteworthy that Jansen fails to disclose the expression of HCN channels in MSCs. This particular deficiency in the teaching of Jansen is not supplemented by the teachings of any of the additionally cited references of the Examiner. As indicated above, Marban and Levy merely teach the expression of dominant negative proteins and, moreover, these references do not even teach the expression of such mutant proteins in MSCs. Regarding Wang, this reference also fails to teach, or suggest, the expression of HCN channels in MSCs. Rather, Wang teaches that MSCs, administered in vivo, are capable of forming gap junctions with native cardiomyocytes and are connected by intercalated disks.

Accordingly, Applicants maintain that even if the cited prior art references were to be combined, they do not teach or suggest all the elements of the claims and thus do not render the claimed invention obvious. Since a combination of the cited references does not teach or suggest all the elements of the claims, Applicants also respectfully submit that the Examiner is impermissibly using hindsight reconstruction in attempting to conjure up the claimed invention from these references. This the courts have consistently warned against, most recently in KSR International v. Teleflex Inc.:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U. S., at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co.* v. *Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964))).

See *KSR International v. Teleflex Inc.*, No 04-1350 at page17 (*U.S.* Apr. 30, 2007).

For at least the above reasons, applicant maintains that the Examiner has failed to establish a *prima facie* case of obviousness, and respectfully request that this ground of rejection be withdrawn.

Rejection of claims 20 and 65 under 35 U.S.C. §103(a) (Obviousness)

The Examiner rejected claims 20 and 65 under 35 U.S.C. §103(a) as allegedly unpatentable over Marban, Jansen, Wang, and Ruhparwar et al. (2002) *Eur J Cardiothorac Surg* 21: 853-857 ("Ruhparwar"). According to the Examiner, Ruhparwar teaches a method comprising administering $2x10^6$ cardiomyocytes directly into the free wall of the left ventricle of X-linked muscular dystrophy-afflicted dogs that fail to express dystrophin in cardiac muscle, and demonstrates electrical and mechanical coupling between allogeneic donor cardiomyocytes and recipient myocardium *in vivo*. The Examiner stated that Ruhparwar emphasizes that cardiomyocytes engraftment could initiate further research aimed at generation of autologous cardiomyocytes preferably from pluripotent embryonic or adult stem cells or by achieving controlled proliferation of adult cardiomyocytes.

The Examiner also acknowledged that Ruhparwar does not teach a composition

comprising MSC comprising HCN2 or a method of using such composition. Nevertheless, the Examiner asserted that it would have been obvious for one of ordinary skill in the art at the time of invention to modify the MSCs that express a nucleic acid encoding specific HCN isoforms as taught by Marban for expressing ion channel genes in a stem cell at a sufficient level for pacemaker activity.

Applicants respectfully disagree. As noted above, none of Marban, Jansen, or Wang disclose, or suggest, a composition comprising MSCs incorporated with a nucleic acid encoding HCN2, wherein the MSC is capable of forming a gap junction with a cell of a mammalian heart in the absence of differentiation of the MSC. Applicants assert that, in teaching the administration of differentiated cardiomyocytes into the heart, Ruhparwar does not remedy the deficiencies of Marban, Jansen, and Wang in this regard. Thus, for at least this reason, Applicants maintain that claims 20 and 65 are not rendered obvious by the combination of Marban, Jansen, Wang, and Ruhparwar. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Double Patenting Rejections

The Examiner maintained the provisional rejection of claims 20, 49-51, 54-57 and 59 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 20-59 of co-pending Application No. 10/342,506 ("the '506 application), which corresponds to U.S. Publication No. 20040137621.

In response, Applicants note that this is a "provisional" rejection over the '506 application which is not an allowed application. Accordingly, if the now pending claims of the subject application are otherwise allowable, the present provisional double patenting rejections should be withdrawn and the claims in the subject application should be allowed and issued, whereby the claims of the '506 application would become subject to an obviousness-type double patenting rejection. At that time, applicant will consider filing a terminal disclaimer, if necessary.

CONCLUSION

In view of the remarks made hereinabove, Applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the February 13, 2007 Office Action, and earnestly solicits allowance of the now pending claims.

If a telephone interview would assist in expediting prosecution of the subject application, the Examiner is invited to telephone the undersigned at the number provided below. No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 11-0600.

Respectfully submitted,
KENYON & KENYON LLP

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Deborah A Somerville
Registration No. 31,995
Carmella L. Stephens
Registration No. 41,328

One Broadway
New York, NY 10004-1007
(202) 425-7200 (telephone)
(212) 425-5288 (facsimile)
Customer No. 26646